

REMARKS

Applicant submits this response to the Office Action dated 26 March 2003. Claims 33, 34, 74-77 and 82-92 are pending in this application. Claims 35-73, 78-81 and 93-95 are deemed withdrawn from further consideration pursuant to the restriction requirement imposed under 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention. Following the above amendments, claims 33, 34, 74-77 and 82-92 have been cancelled without prejudice and new claims 96-110 have been added. Applicant submits that each of these amendments is supported by the specification as filed and no new matter has been added. It is also noted that applicant has not abandoned the cancelled subject matter, but reserve the right to file the same in a continuation application. Moreover, applicant reserves the right to file the non-elected claims in a divisional application.

At the outset, before addressing the merits of the issues raised by the Office Action, it is to be noted that the designation of the Office Action referred to herein as a Final Office Action is in error, since this is the first substantive Office Action on the merits raised in the above-identified application. Examiner Tate was so notified in a teleconference on April 2, 2002, and acknowledged the error, indicating that he will be withdrawing the finality of the Office Action.

Rejection Under 35 U.S.C. § 112, first paragraph, enablement

Claims 33, 34, 74-89 and 94-99 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected to make and/or use the present invention. Specifically, the Office Action alleges that the specification, while being enabling for stimulating the

immune system of a human subject *via* the administration of an effective amount of an angeloyl-substituted ingenane or salt thereof obtained from one of the three demonstrated/disclosed *Euphorbia* plant species, but further alleges that the specification does not reasonably provide enablement for stimulating the immune system of a subject using any or all compounds, including any or all derivatives of angeloyl-substituted ingenane, obtained from any other *Euphorbia* plant species.

Applicant respectfully traverses this ground of rejection. Applicant respectfully submits that the United States Patent and Trademark Office has not met its burden establishing that the application is non-enabling. In order to make a proper rejection, the Office Action has the initial burden to establish a reasonable basis to question the enablement for the claimed invention In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1515 (Fed. Cir. 1993). Case law has held that the specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for an enabling support. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the Marzocchi Court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the

trouble and expense of supporting his presumptively accurate disclosure.” 439 F.2d at 224, 169 USPQ at 370.

Here, the Office Action has not provided any rationale supporting its allegation that the full scope of the present invention is not enabled. In particular, the Office Action has not cited any reference which refutes the teaching of the present invention. Moreover, the Office Action has not provided any evidence which disputes the allegation of the utility of the present invention. The Office Action just renders a mere conclusion without providing any evidence whatsoever that supports its belief that any angeloyl substituted ingenane or derivatives thereof derived from any Euphorbia plant species other than the three identified in the Office Action would not be useful for stimulating the immune system. Without such evidence, the Office Action has improperly shifted the burden to the applicant.

Moreover, contrary to the allegations of the Office, the application is enabling. More specifically, Applicant respectfully submits that the present application is replete with guidance on how one of ordinary skill in the relevant art would stimulate the immune system of a human subject *via* the administration of an effective amount of an angeloyl-substituted ingenane or salt thereof from any *Euphorbia* plant species. Applicant has described in detail, how one of ordinary skill in the relevant art could isolate an angeloyl-substituted ingenane from a *Euphorbia* plant species using routine methodologies, such as HPLC purification, for example, see Examples 1, 2, 3, 4, 6, 7, 8, 9, 10, 11 and 14 for guidance. As further evidence, applicant submits an executed Declaration under 37 C.F.R. §1.132 by the inventor Dr. James Aylward, attached hereto as Exhibit A which was submitted in copending application 09/888,198. The Declaration shows how one of ordinary skill in the art, using the methodologies described in the present specification, were able to isolate various angeloyl-

substituted ingenanes from *Euphorbia paralias*. More specifically, the Declaration of Dr. James Aylward describes how, using HPLC purification, a total of sixteen (16) angeloyl-substituted ingenanes were identified from *paralias*. Applicant, therefore, submits that one of ordinary skill in the relevant art would be able to identify angeloyl-substituted ingenanes from additional *Euphorbia* species without undue experimentation.

Having identified an angeloyl-substituted ingenane, one of ordinary skill in the relevant art could then determine, based on the teachings provided in the subject specification, if the isolated angeloyl-substituted ingenane was immunostimulatory. The present specification is replete with *in vitro* assays on how one would test an angeloyl-substituted ingenane to ascertain its immunostimulatory properties. For example, Example 13 describes *in vitro* assays, wherein angeloyl-substituted ingenane or compositions comprising angeloyl-substituted ingenanes are cultured with MM96L cells. mRNA isolated from these cells were then analyzed using array technology. A number of molecules relevant to enhancing an immune response were induced, particularly G-SCF and MHC molecules tested against tumor cell lines for their anti-cancer activity. Further, Example 15 describes experiments where culturing T cells in the presence of crude *E. peplus* sap induced proliferation of T cells.

Thus, given the level of illustrative guidance in the specification as originally filed, which is supported by the attached Declaration of Dr. James Aylward, Applicant respectfully submits that the skilled artisan could readily practice the presently claimed methods of stimulating the immune system of a subject via the administration of an effective amount of an angeloyl-substituted ingenane or salt thereof from any *Euphorbia* plant species without undue experimentation.

It is to be noted that the Office Action acknowledges that the present specification is enabling for stimulating the immune system *via* the administration of an effective amount of an angeloyl-substituted ingenane or salt thereof obtained from one of the three demonstrated/disclosed *Euphorbia* plant species. Applicant submits that the angeloyl substituted ingenane from the three identified Euphorbia plants are representative of the present invention and evidence the efficacy of the full scope of the present invention. Angeloyl substituted ingenanes are angeloyl substituted ingenanes regardless of the source. Thus, one of ordinary skill in the art reading the application would understand that the angeloyl substituted ingenane from any Euphorbia plant species would be useful stimulating the immune system. Applicant accordingly submits that the pending claims are fully enabled under 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejection is thus respectfully requested.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 33, 34, 74-89 and 94-99 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Examiner alleges that claim 33 is rendered vague and indefinite for reciting the phrase "is capable of inhibiting". Applicant submits that as claim 33 has been cancelled, and newly added claim 96 corresponding to claim 33 does not recite the phrase "is capable of inhibiting", this rejection is now rendered moot. Reconsideration and withdrawal of the rejection is thus respectfully requested.

The Examiner also alleges that claims 74-77 are rendered vague and indefinite by the phrase "an angeloyl substituted derivative". Applicant respectfully traverses this ground of rejection. However, for purposes of clarity only, Applicant has elected to cancel claims 74-77 at this time, and added new claims 100 to 102 corresponding thereto which recites in part "wherein the derivative of an angeloyl-substituted ingenane is defined as an acetylated derivative". For the convenience of the United States Patent and Trademark Office, Applicant has submitted a second Declaration under 37 C.F.R. §1.132 by Dr. James Aylward attached hereto as Exhibit B which was also previously submitted in copending U.S. Patent application no. 09/888,178. The Second Declaration describes the acetylation of ingenanes. Based thereon Applicant respectfully submits that one of ordinary skill in the relevant art would understand the metes and bounds of what was meant by the phrase "an angeloyl substituted derivative" in these claims. Reconsideration and withdrawal of the rejection is thus respectfully requested.

The Examiner further alleges that claim 74 is rendered vague and indefinite for the phrase "wherein the compound comprises a composition selected from", alleging that the recited compounds thereafter are not compositions per se, but compounds. Applicant submits that as claim 74 has been cancelled, this rejection is now rendered moot. Reconsideration and withdrawal of the rejection is thus respectfully requested.

Moreover, the Examiner alleges that claims 83-90 are vague and indefinite for recitation of the phrase "capable of". Applicant respectfully traverses this ground of rejection. However, Applicant has elected to cancel claims 83-90 at this time, rendering the present rejection moot. Moreover, the phrase "capable of" is not recited in any of the claims pending

in the above-identified application. Reconsideration and withdrawal of the rejection is thus respectfully requested.

In addition, the Examiner alleges that claim 94 is vague and indefinite with respect to the recitation of the phrase "wherein the compound further comprises a beta-alanine betaine or a hydroxy-dimethyl proline". Applicant respectfully traverses this ground of rejection. However, Applicant has elected to cancel claim 94 at this time, rendering the present rejection now moot. Reconsideration and withdrawal of the rejection is thus respectfully requested.

Rejection Under 35 U.S.C. §102(b)

Claims 33, 34, 74-77 and 83-91 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Zayed *et al.* (J. Cancer Res. Clin. Oncol., 1998) or by Abo (Fitoterapia, 1988), with evidence provided by Benjamini *et al.* (Immunology-A Short Course).

The present specification is drawn, inter alia, to a method of stimulating the immune system in a subject comprising administering an isolated compound selected from an angeloyl-substituted ingenane or salt thereof obtained from the sap of a *Euphorbia species* and an active derivative of an angeloyl-substituted ingenane or salt thereof obtained from the sap of a *Euphorbia species*.

Zayed *et al.* teach administering a compound comprising one of various angeloyl-substituted ingenane compounds and derivatives thereof to goats, as well as to mouse ears which are administered within a milk extract or separately. Abo disclose administering an angeloyl-substituted ingenane compound to mouse ears (within a

pharmaceutical carrier Me₂CO) to assess skin irritation. Applicants respectfully traverse this ground of rejection. As the Office Action indicates, neither reference discloses the use of an isolated compound. However, the compound being administered must be an isolated compound for use in a human subject. It is well recognized that anticipation requires that the referenced publication disclose each and every element of the claim. The absence of even one claimed element from the cited publication negates anticipation. Kalman v. Kimberly Clark Corp., 713 F.2d 760, 771-772 218 USPQ 781, 789 (Fed. Cir. 1983). Since the cited publications do not teach or disclose an isolated compound, the cited publications do not anticipate the claimed subject matter. Accordingly, Applicant respectfully requests that this rejection under 35 U.S.C. §102(b) is obviated; withdrawal thereof is respectfully requested.

Claims 33, 34, 74-77 and 83-91 stand rejection under 35 U.S.C. § 102(b) as allegedly being anticipated by Hecker *et al.* (U.S. Patent No. 4,716,179). The claimed subject matter is drawn, inter alia, to a method of stimulating the immune system of a subject *via* administering an isolated compound selected from the group consisting of an angeloyl-substituted ingenane obtained from the sap of an *Euphorbia* species. Hecker *et al.* teach treating a solid tumor *via* administering an antineoplastic composition which comprises an effective amount of a non-irritating or slightly irritating compound obtained from a *Euphorbia* plant including one of various ingenane compounds and derivatives thereof. The Office Action alleges that the various claimed functional effects would be inherent in the referenced compound derivatives.

Applicant respectfully traverses this ground of rejection. Hecker *et al.* do not teach or suggest an angeloyl substituted ingenane. Although some ingenanes are tested, these are not angeloyl substituted, a feature required by the present claims. The Hecker *et al.*

reference focuses on the treatment of cancer using an effective amount of a phorbol which has a completely different ring structure than ingenol. Thus, they cited publication does not teach or disclose an ingenol, let alone an angeloyl ester of ingenol, as claimed.

As Hecker *et al.* do not teach or suggest an angeloyl substituted ingenanes, as presently claimed, if Applicant respectfully submits that it does not teach the use of angeloyl substituted ingenanes as claimed. Accordingly, the Hecker *et al.* citation does not include each and every limitation of the present claim and therefore cannot anticipate the claimed invention.

Thus, for the reasons provided, this rejection of the claimed subject matter under 35 U.S.C. §102(b) is overcome; withdrawal thereof is respectfully requested.

Claims 33, 34, 74-77, 84, 85, 89, 93 and 95-98 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Tamas (European Patent No. 0 330 094). Specifically, the Office Action alleges that Tamas teaches treating malignant and non-malignant tumors using an ethanolic extract of *Euphorbia hirta*. According to the Office Action, the present specification discloses that the angeloyl substituted ingenanes or salts thereof can also be derived from *Euphorbia hirta* via, for example, ethanol extraction. The Examiner concludes that the claimed compound would inherently be present within the ethanol extract described in the referenced publication.

Applicant respectfully traverses this ground of rejection. Applicant submits that nowhere does the Tamas reference teach, suggest or even allude to the use of an angeloyl-substituted ingenane or derivative thereof. The Office Action alleges, however, that the claimed compound would inherently be present within the

ethanol extract described in the cited publication. But, this is not the case. According to M.P.E.P. § 2112:

“The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic”

M.P.E.P § 2112, further states that the burden to establish that a certain result or characteristic may occur rests with the United States Patent and Trademark Office.

Applicant submits that the United States Patent and Trademark Office has not met its burden of providing evidence which establishes that the compounds of the present invention, namely angeloyl-substituted ingenanes or derivatives thereof, would be present within the ethanol extract. Nor has the United States Patent and Trademark Office established that the therapeutic effects of the composition described in the Tamas reference was attributable to angeloyl-substituted ingenanes, rather than an additional component in the ethanol extract used. Accordingly, the cited publication does not teach explicitly or implicitly the use of angeloyl-substituted ingenanes for stimulating the immune system in a human subject. Moreover, Tamas does not teach or disclose the use of or administration of an isolated compound, as claimed; a portion with which the Office Action concurs. Consequently, Tamas does not teach or disclose all of the claimed elements. Thus, for these reasons, this rejection under 35 U.S.C. §102(b) is obviated; withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 33, 34, 74-77 and 82-92 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hecker *et al.* Applicant respectfully traverses this rejection and reiterates the comments hereinabove made in reference to the rejection under 35 U.S.C. §102(b) citing Hecker, et al.. As described hereinabove, Hecker et al. disclose the use of compounds which are structurally quite different from the angeloyl substituted ingenane or derivatives thereof, which are recited in the claims. It only discloses the use of phorbol derivatives which are structurally quite different from the compounds used in the present invention and do not render obvious the compounds utilized in the present invention. The comments hereinabove discussing the §102 rejection of the claims citing Hecker, et al. are incorporated by reference. Consequently, the rejected claims are patentable thereover. Withdrawal of this rejection is respectfully requested.

Claims 33, 34, 74-89 and 94-99 stand rejected under 35 U.S.C § 103(a) as allegedly being unpatentable over Tamas and El-Mezabani *et al.* (Planta Med., 1979). Applicant reiterates the comments hereinabove made in relation to the Tamas reference under 35 U.S.C. § 102(b) and incorporate the same by reference. It is respectfully submitted that the Examiner has not made out a prima facie case under 35 U.S.C. §103, as the Official Action has not shown that the therapeutic effect of the compositions described in the Tamas reference was attributable to any angeloyl substituted ingenane rather than to some other component therein. Moreover, Tamas does not teach, disclose or suggest an isolated compound, as claimed - - a position with which the United States Patent and Trademark Office concurs.

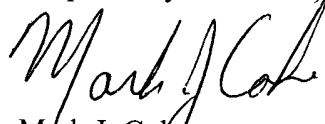
The secondary reference does not overcome the deficiency of the primary references. In fact, it suffers from the same problem as the primary reference. More specifically, it does not teach, disclose or even suggest that an ingenane - - let alone an

angeloyl substituted ingenane or its derivative - - is useful for treating cancer. The Office Action has assumed that the secondary reference (as well as the primary reference) inherently disclose the use of angeloyl substituted ingenane, but without any basis, as there is no teaching or suggestion therein for one of ordinary skill in the art to so conclude. Moreover, just like the primary reference, this publication does not teach, disclose or suggest an isolated compound - - a position with which the Office Action concurs.

Thus, the combination of two references which do not specify the compounds therein fails to disclose or suggest the use of angeloyl substituted ingenane or derivatives thereof, as claimed. Moreover, the combination does not teach, disclose or suggest the use of a isolated compound, as claimed. Therefore, the rejection of the above-identified claims under 35 U.S.C. §103 is overcome; withdrawal thereof is respectfully requested.

Thus, all of the remaining claims in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,


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